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The effect of enteral nutrition in colorectal surgery

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General summary and discussion

In spite of improvements in perioperative care, the incidence and burden of postoperative complications in colorectal surgery remains substantial.[1,2] A balanced surgical stress response is crucial for optimal recovery and to reduce complications such as postoperative ileus (POI).[3] Previous studies demonstrated a beneficial effect of enteral nutrition on POI and surgical stress. Specifically, vagal nerve stimulation by means of lipid-enriched enteral nutrition reduced inflammation and POI in experimental studies[4], while in a clinical setting POI and anastomotic leakage (AL) were reduced by means of sham feeding[5] and early postoperative enteral nutrition.[6] In this thesis, we further investigated the role of enteral nutrition in the development of complications and the surgical stress response following colorectal surgery.

In **Chapter 2** we performed a systematic review and meta-analysis to study existing literature on the effects of early enteral nutrition on AL. We found that most existing trials were of limited methodological quality, and definitions of AL varied greatly. Pooling of all available data demonstrated a reduction of AL by means of early start of enteral nutrition. However, after excluding trials with a risk of bias in the sensitivity analysis, this effect was no longer significant. Taken together, this study showed that high-quality studies are needed to further study the effects of enteral nutrition on AL in a clinical setting.

In a prospective, randomized controlled study, patients undergoing major surgery for locally advanced or recurrent rectal cancer were allocated to receive supplementary early enteral versus parenteral nutrition in addition to a regular oral diet. Patients in the enteral group experienced less POI and less AL as compared to the parenteral group.[6] It was hypothesized that the observed effects of early enteral nutrition on clinical outcomes may be explained by an effect on plasma amino acid concentrations. Chapters 3, 4, and 5 are preplanned substudies of this trial. In **Chapter 3**, plasma concentrations of conditionally essential amino acids (i.e. glutamine, citrulline, and arginine) were compared between the two groups. It was found that plasma concentrations of glutamine and arginine were lower in the enteral group on postoperative day 1 and 5, whereas a better clinical outcome was observed as compared to the parenteral group. These findings suggest that plasma glutamine or arginine concentrations were not important determinants of clinical outcome, and that the benefit of enteral nutrition may have other mechanisms. Furthermore, these results are in line with other studies showing that supplementing specific amino acids may not necessarily result in improved clinical outcomes, or may even be harmful in specific patient groups.[7-12]

In **Chapter 4**, changes in anti-oxidative amino acids (taurine, glutamic acid, glycine, N-acetylcysteine, and hydroxyproline) were compared between patients receiving supplementary enteral versus parenteral nutrition undergoing rectal surgery.[6] It

was found that postoperative glycine concentrations were significantly higher in the parenteral group, while other amino acid concentrations were similar between groups. This may be due to the higher amounts of glycine administered in the parenteral group. Multivariable regression analysis showed no association between plasma amino acid concentrations and clinical outcomes. Again, these findings are in line with results of other studies that show no benefit of supplementing amino acids in a clinical setting.[12,13] As such, in accordance with the results from Chapter 3, postoperative plasma amino acid concentrations did not provide a causal explanation for the observed benefits of enteral nutrition. It may be postulated that lower plasma amino acid concentrations are to be considered as an epiphenomenon of surgical trauma, rather than an actual contributor to impaired postoperative recovery. Of note, these studies were limited by the fact that the original trial[6] was not powered to detect differences in plasma amino acid concentrations.

In **Chapter 5** it was investigated whether an effect on the inflammatory or metabolic stress response could explain the beneficial effect of enteral nutrition as observed in the original trial.[6] Here, markers of surgical stress (C-reactive protein and albumin) were determined as well as markers of postoperative insulin resistance (Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) by means of plasma glucose and insulin concentrations). On postoperative day (POD) 1, albumin concentrations were lower while C-reactive protein concentrations were higher in the enteral group, suggesting a greater surgical stress response when compared to the parenteral group. These early postoperative differences may be explained by the fact that the enteral group experienced a greater degree of surgical trauma and concomitant fluid resuscitation, as reflected by the longer operating time and greater amounts of operative blood loss in this group, and discussed by the authors in the original paper.[6] Patients in the parenteral group demonstrated higher insulin concentrations and HOMA-IR scores on POD5, indicating a greater magnitude of metabolic dysregulation as compared to the enteral group. Further analysis revealed that significantly more calories were cumulatively provided via the parenteral route as compared to the enteral route, which may have induced caloric overfeeding. These findings are in line with other studies that suggest an improved metabolic response by means of enteral nutrition when compared to parenteral nutrition.[14-19] Caloric overfeeding and the subsequent detrimental effects on clinical outcomes (e.g. increased risk of infectious complications) is now a well-known complication of parenteral feeding.[20] Interestingly, when overfeeding is prevented by maintaining normocaloric feeding goals, a recent trial showed no differences in clinical outcomes between enteral versus parenteral nutrition in critically ill patients.[21] As such, changes in metabolic dysregulation may partially explain the differences in clinical outcomes between the two groups in the original trial.[6] However, in this study cohort increased markers of metabolic stress were not

associated with clinical outcomes. Taken together, patients in the parenteral group may have experienced a greater degree of caloric overfeeding and metabolic dysregulation, however this likely does not explain the beneficial effect of enteral nutrition.

Myopenia is another factor that can impair recovery following colorectal surgery by increasing the early surgical stress response. In **Chapter 6**, presence of myopenia in patients undergoing colorectal surgery was investigated by means of quantifying skeletal muscle mass via computed tomography images at the third lumbar vertebra. For this study, data was analyzed from patients from a previous randomized trial, in which the effect of perioperative gum chewing on specific markers of the systemic inflammatory response was studied.[5] Almost 40% of the included patients in this cohort were myopenic and demonstrated significantly higher plasma concentrations of interleukin-8 (IL-8) when compared to patients without myopenia four hours after start of surgery. However, this pro-inflammatory effect of myopenia was no longer significant after exclusion of four patients that demonstrated increased preoperative IL-8 concentrations. No effect of myopenia was observed on concentrations of C-reactive protein or soluble tumor necrosis factor receptor 1. Taken together, the finding that myopenia may increase some, but not all, markers of systemic inflammation was limited by the presence of confounders and small patient cohort size, underlining the need for further studies with larger sample sizes.

Experimental studies have previously demonstrated a reduction of POI and AL by means of enteral nutrition. Timing and composition were essential; lipid-enriched nutrition given just before, during, and directly after surgery provided the optimal effect. To further study this concept, an international, multicenter, double-blind, randomized controlled trial was performed to test the effects of perioperative lipid-enriched enteral nutrition on POI and AL in a clinical setting (**Chapter 7** and **8**). Patients undergoing elective, colorectal resection with primary anastomosis were included. Via a branched, double-blind tube feeding system, lipid-enriched enteral nutrition was administered either to the patient via a nasojejunal tube, or to a blinded black box that was attached to the bed. Continuous feeding was administered from three hours before until six hours after surgery in all patients. In contrast to experimental findings, no effect of perioperative lipid-enriched enteral nutrition was seen on POI, AL or any other complication. The lack of effect was unexpected but may be explained by important differences in study design. In contrast to previous studies[5,6], the combined use of laparoscopy and overall good adherence to ERAS protocols in the current trial may have attenuated the surgical stress response to such an extent that the effect of perioperative nutrition was no longer measurable.[22-27] However, this needs to be clarified further in additional studies.

In **Chapter 9**, current nutritional interventions to reduce POI were reviewed. Importantly, it was found that nutritional interventions from experimental studies were not effective in a clinical setting. Alternative strategies to reduce POI by mitigating inflammation, such as electrical vagal nerve stimulation[28], may be promising but are yet to be tested in a clinical setting.

Future perspectives

To improve postoperative outcomes in colorectal surgery, optimizing the surgical stress response by attenuating early postoperative inflammation may be essential. In this light, the results from this thesis show that in patients who are treated by means of modern surgical protocols including laparoscopy and ERAS, perioperative lipid-enriched enteral nutrition has no additional benefit in terms of postoperative complications, in contrast to results from previous experimental studies. It may be postulated that perioperative lipid-enriched nutrition could be effective when postoperative inflammation and risk of POI is greater, for example in patients undergoing multivisceral resections with hyperthermic intraperitoneal chemotherapy (HIPEC).[29] However, this is yet to be further investigated. Alternatively, methods of direct vagus nerve stimulation may be more effective in reducing early inflammation and improving outcomes. For example, electrical stimulation of the vagus nerve has been shown to significantly reduce systemic inflammation in both murine and human subjects.[28] However, a concomitant reduction of POI has only been observed in mice.[28] A clinical trial on the effects of electrical vagus nerve stimulation is currently ongoing (NCT 02524626), and should demonstrate whether this is a safe and effective intervention to reduce POI in the surgical population. Lastly, other strategies aimed at optimizing patient status and attenuating surgical stress may further improve postoperative outcomes. Such strategies could include preoperative prehabilitation with physiotherapy and nutritional counseling[30], and are currently being investigated in various surgical groups.[31-33]

Another way to improve perioperative care can be to further study the role of postoperative inflammation and other potentially pathogenic factors in surgical convalescence.[34] To this end, various biological samples were obtained from patients in the SANICS II trial as secondary outcomes. These include pre- and postoperative plasma inflammatory markers, peritoneal lavage samples, full-thickness colonic tissue samples, and pre- and postoperative fecal samples. In particular, perioperative changes in the gut microbiome will be studied in fecal samples and colonic tissue samples, since cumulative evidence suggests that changes in the gut microbiome play an important role in the recovery from gastrointestinal surgery, development of postoperative complications including AL and POI, and even in cancer recurrence.[35-40] Furthermore, there is some evidence

suggesting that there may be genetic predispositions for impaired wound healing that can make a patient prone to develop AL or other complications.[41,42] Future research will be necessary to substantiate these results.

Nederlandse samenvatting

De incidentie van naadlekkage en postoperatieve ileus na colorectale chirurgie blijft relatief stabiel, ondanks verbeteringen in de perioperatieve zorg de afgelopen jaren. Eén van de verbeteringen die de afgelopen jaren is doorgevoerd is het snel starten van enterale voeding na de operatie, in het kader van versneld herstel (ERAS) programma's. Zowel de timing van het geven van voeding alsmede de samenstelling zouden van belang kunnen zijn bij het verminderen van complicaties. In experimentele en preklinische studies werd aangetoond dat vetrijke enterale voeding gegeven juist voor en direct na een operatie minder inflammatie en minder postoperatieve ileus geeft door activatie van de nervus vagus. In een eerdere klinische studie werd aangetoond dat de incidentie van postoperatieve ileus en naadlekkage kan worden verminderd door direct starten van enterale voeding na uitgebreide rectumchirurgie. Daarnaast liet een andere klinische studie zien dat het risico op postoperatieve ileus en naadlekkage kan worden verminderd door het geven van kauwgom (om de nervus vagus te stimuleren) juist voor en direct na een operatie. In dit proefschrift is onderzocht of enterale voeding rondom een operatie postoperatieve ileus en naadlekkage kan verminderen en welke metabole effecten het geven van vroege enterale voeding heeft.

In **Hoofdstuk 2** is in bestaande literatuur systematisch onderzocht wat het effect is van enterale voeding op het ontstaan van naadlekkage na colorectale chirurgie. Het merendeel van de bestaande studies waren van matige methodologische kwaliteit, en de gebruikte definities van naadlekkage varieerden aanzienlijk. In de meta-analyse was vroeg starten van postoperatieve enterale voeding geassocieerd met een kleiner risico op naadlekkage. Echter na het excluderen van studies met risico op bias was dit gunstige effect niet langer significant. Concluderend liet deze studie zien dat er meer onderzoek van goede methodologische kwaliteit nodig is om te bepalen wat het effect van enterale voeding is op naadlekkage in een klinische setting.

In een eerdere studie van Boelens et al. werd aangetoond dat vroege enterale voeding (ten opzichte van parenteriale voeding) in patiënten die majeure rectale chirurgie ondergingen, leidde tot significant minder postoperatieve ileus en naadlekkage.[1] Uit eerder onderzoek bleek dat metabole veranderingen een mogelijke verklaring zouden kunnen zijn voor dit effect. In **Hoofdstuk 3** en **4** werd onderzocht of dit gunstige effect van enterale voeding een gevolg was van verschillen in plasma concentraties van klinisch relevante aminozuren, te weten glutamine, citrulline, arginine, taurine, glycine, glutaminezuur, N-acetylcysteine, en hydroxyproline. In de enterale groep waren plasma concentraties van glutamine, arginine, en glycine postoperatief lager in vergelijking met de parenterale groep,

terwijl de enterale groep minder complicaties had. Er werd geen verschil gezien in de overige aminozuurconcentraties, noch werd er een associatie gezien tussen plasma concentraties van aminozuren en postoperatief herstel. Deze studies toonden aan dat het gunstige effect van enterale voeding niet kon worden verklaard door verschillen in aminozuurconcentraties. In **Hoofdstuk 5** werd onderzocht of het gunstige herstel in de enterale groep kon worden verklaard door een effect van voeding op postoperatieve inflammatie of insulineresistentie. Voor dit onderzoek werden markers van inflammatie (albumine en C-reactief proteïne) en van insuline-resistentie (Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) waarden) vergeleken tussen beide groepen. Op postoperatieve dag 1 waren plasma concentraties van albumine lager en van C-reactief proteïne hoger in de enterale groep, wat duidt op een groter inflammatoire respons. Dit kan mogelijk verklaard worden door de grotere hoeveelheid bloedverlies en langere operatieduur in de enterale groep, zoals beschreven door de auteurs in het oorspronkelijke artikel. Op postoperatieve dag 5 hadden patiënten in de parenterale groep meer calorieën toegediend gekregen, en hadden hogere insuline concentraties en HOMA-IR scores, wat duidt op een grotere metabole ontregeling en mate van insulineresistentie in vergelijking met de enterale groep. Deze resultaten kwamen overeen met andere studies waarin werd aangetoond dat parenterale voeding vaker gepaard gaat met calorische overvoeding en metabole ontregeling, wat kan leiden tot een hogere risico op bijvoorbeeld infectieuze complicaties. Echter, de mate van metabole ontregeling was in deze studiegroep niet geassocieerd met klinische uitkomsten. Concluderend lijkt de mate van metabole ontregeling groter te zijn geweest in de parenterale groep, hoewel dit mogelijk niet van groot effect is geweest op het algemeen postoperatief herstel en dus niet verklarend is voor het betere herstel in de enterale groep.

De aanwezigheid van myopenie (i.e. verminderde skeletspiermassa) is een andere factor die mogelijk het postoperatief herstel kan vertragen door de vroege postoperatieve inflammatoire respons te beïnvloeden. In **Hoofdstuk 6** werd de aanwezigheid van myopenie onderzocht in patiënten die een colorectale resectie hadden ondergaan, door de skeletspiermassa te meten op preoperatieve computertomografie-scans. Hiervoor werd data gebruikt van een eerder uitgevoerde studie, waarin patiënten waren gerandomiseerd tot perioperatief kauwgom kauwen versus placebo, en pre- en postoperatieve inflammatie markers waren gemeten.[2] Patiënten met myopenie hadden postoperatief significant hogere interleukine-8 concentraties in vergelijking met patiënten zonder myopenie. Dit verschil was niet meer zichtbaar na exclusie van patiënten die preoperatief reeds verhoogde interleukine-8 concentraties hadden. Er werd geen verschil gezien in concentraties van andere inflammatie markers (C-reactief proteïne of oplosbaar tumor necrose factor receptor 1). De bevinding dat myopenie mogelijk

geassocieerd is met een sterkere verhoging van enkele, maar niet alle postoperatieve inflammatie markers, kan dus ook te wijden zijn aan de relatief kleine studiegroep en confounders. Meer onderzoek met grotere patiëntgroepen is nodig om hier meer duidelijkheid in te verkrijgen.

In eerder experimenteel onderzoek werd aangetoond dat het risico op postoperatieve ileus en naadlekkage kan worden verminderd met behulp van enterale voeding. De samenstelling en timing waren hierbij essentieel; vetrijke voeding welke toegediend wordt vlak vóór, tijdens, en direct ná chirurgie gaf het meest gunstige effect. Dit effect van vetrijke perioperatieve enterale voeding op postoperatieve ileus en naadlekkage werd in een klinische setting verder onderzocht in een internationaal, multicenter, dubbelblind gerandomiseerd onderzoek (**Hoofdstuk 7** en **8**). Tweehonderdtachtig patiënten die een electieve, colorectale resectie met primaire anastomose ondergingen werden geïncludeerd. Vetrijke voeding werd op een dubbelgeblindeerde wijze toegediend middels een gesplitst, ondoorzichtig sondevoedingssysteem óf aan de patiënt via een nasojejunale sonde, óf aan een geblindeerde doos die aan het bed van de patiënt werd bevestigd. Bij alle patiënten werd de voeding 3 uur vóór de operatie gestart, en liep continu door tot 6 uur ná de operatie. In tegenstelling tot eerder pre-klinisch onderzoek werd er geen effect van vetrijke perioperatieve enterale voeding gezien op postoperatieve ileus, naadlekkage, of andere klinisch uitkomsten. Het uitblijven van een significant effect kan mogelijk verklaard worden door belangrijke verschillen tussen de huidige studie-opzet en eerdere studies. Het veelvuldig gebruik van laparoscopische chirurgie en goede compliantie aan ERAS protocollen kan mogelijk de chirurgische stress respons reeds dusdanig hebben geminimaliseerd dat een effect van vetrijke voeding niet langer meetbaar was. Aanvullend onderzoek zal hier meer duidelijkheid over moeten verschaffen.

In **Hoofdstuk 9** werd een overzicht gegeven van bestaande voedingsinterventies gericht op het verminderen van postoperatieve ileus. Van belang was dat effectieve interventies uit pre-klinische studies niet werkzaam bleken in een klinische setting. Andere therapieën tegen postoperatieve ileus zoals elektrische stimulatie van de nervus vagus worden op dit moment onderzocht in klinische studies.